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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/507,129	04/11/2005	Satoshi Saito	03419.0023-00	8898

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EXAMINER	
LONG, SCOTT	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/507,129	SAITO ET AL.	
	Examiner	Art Unit	
	SCOTT LONG	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 16-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 16-18* is/are rejected.

7)☐ Claim(s) ____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/18/2008 has been entered.

Claim Status

Claims 1-7 and 16-18 are pending. Claims 1 and 16 are amended. Claim 8-15 and 19 are cancelled. Claims 1-7 and 16-18 are under current examination.

Priority

This application claims benefit as a 371 of PCT/JP03/02833 0 (filed 3/11/2003). This application also claims benefit from the foreign application JAPAN 2002-065880 (filed 03/11/2002). The applicant has provided an English translation of the foreign application JAPAN 2002-065880. Therefore, the instant application has been granted the benefit date, 3/11/2002, from the foreign application JAPAN 2002-065880.

Response to Arguments - Claim Rejections 35 USC 112

Response to Arguments – Written Description (35 USC 112, 1st paragraph)

The rejection of claims 1-7 under 35 USC 112, first paragraph (written description) is withdrawn in response to the applicant's claim amendments and arguments.

Applicant's arguments (Remarks, pages 8-10) and Claim amendments, filed 18 June 2008, with respect to claims 1-7 have been fully considered and they are persuasive.

The applicant has amended the scope of the instant claims to bacterial and yeast transformants. This amendment makes the examiner's rejection moot.

Therefore, the examiner hereby withdraws the rejection of claims 1-7 under 35 USC 112, first paragraph (written description).

Response to Arguments - Claim Rejections 35 USC § 102

The rejections of claims 1-4, 6-7 and 16-18 as anticipated by Porro et al (US-6429006) under 35 USC 102(e) and by Porro et al. (WO99/14335) as anticipated under 35 USC 102(b) are withdrawn in response to the applicant's claim amendments and arguments.

Applicant's arguments (Remarks, pages 21-22) and Claim amendments, filed 18 June 2008, have been fully considered and they are persuasive.

The applicant has amended the scope of the instant claims so that the pyruvate decarboxylase gene on the host chromosome is replaced with the exogenous lactate dehydrogenase gene." This amendment makes the examiner's rejection moot.

Therefore, the examiner hereby withdraws the rejection of claims 1-4, 6-7 and 16-18 under 35 USC 102.

NEW GROUNDS OF REJECTION

Claim Rejections 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-7 and 16-18 are rejected under 35 U.S.C. 103(a) as being obvious over Porro et al. (WO99/14335).

Claim 1 is directed to a bacterial or yeast transformant into which has been incorporated a DNA for coding a foreign protein having lactate dehydrogenase activity and provided with pyruvic acid substrate affinity that equals or exceeds the pyruvic acid substrate affinity of the pyruvate decarboxylase inherent in the host organism, wherein the DNA for coding the aforementioned foreign protein has been controllably incorporated such that it is under the control of the genome promoter of the pyruvate decarboxylase gene on the host chromosome, or such that it is under the control of a structural and functional homologue of the genome promoter of the pyruvate decarboxylase gene, which replaces the genome promoter of the pyruvate decarboxylase gene on the host chromosome, and wherein the pyruvate decarboxylase gene on the host chromosome is replaced with the DNA for coding the foreign protein having lactate dehydrogenase activity. Porro et al. teach, "yeast strains…transformed with at least one copy of a gene coding for lactic dehydrogenase (LDH) functionally linked to promoter sequences allowing the expression of said gene in yeasts" (page 4, lines 6-11). Porro et al. teach, "yeast strains having…a reduced pyruvate decarboxylase activity and transformed with…a gene coding for lactic dehydrogenase (LDH) functionally linked to promoter sequences" (page 4, lines 12-17). Porro et al. teach any yeast promoter…may be used according to the invention…the promoter of

pyruvate decarboxylase gene of K. lactis (KlPDC) is particularly preferred (page 14, lines 18-28). Porro et al. further teach, "Pyruvate decarboxylase gene promoters…are particularly preferred" (page 15, lines 2-5). Porro et al. describe making a triple deletion of the pyruvate decarboxylase genes encoding PDC1, PDC5, and PDC6, using homologous recombination (page 8, lines 25-27). Porro et al. further teach that "PDC genes are highly conserved among different yeast genera" (page 9, lines 7-9). Porro et al. also teach "integrative vectors can be obtained by using homologous DNA sequences in certain regions of the host genome, allowing, by homologous recombination, integration of the vector" (page 12, lines 12-15).

Claim 2 is directed to the transformant according to claim 1, wherein the aforementioned foreign protein is a bovine-derived lactate dehydrogenase or its homologue. Porro et al. teach, "the gene coding for lactate dehydrogenase may be of any species (e.g. mammalian, such as bovine)" (page 9, lines 29-30).

Claim 3 is directed to the transformant according to claim 1, wherein the aforementioned foreign protein is a protein comprised of the amino acid sequence shown in sequence number 1 or its homologue. SEQ ID NO:1 is the bovine lactate dehydrogenase gene. Clearly, Porro et al. contemplates the amino acid encoded this gene or its homologue. Porro et al. teach, "the gene coding for lactate dehydrogenase may be of any species (e.g. mammalian, such as bovine)" (page 9, lines 29-30).

Claim 4 is directed to the transformant according to claim 3, wherein the aforementioned foreign protein is coded by the DNA sequence shown in SEQ ID NO: 3. Clearly, Porro et al. contemplates this gene or its homologue. Porro et al. teach, "the

gene coding for lactate dehydrogenase may be of any species (e.g. mammalian, such as bovine)" (page 9, lines 29-30). SEQ ID NO:3 is a homologue of bovine lactase dehydrogenase which has been codon optimized for expression in Saccharomyces cerevisiae.

Claim 5 is directed to the transformant of claim 4, having the DNA sequence shown in SEQ ID NO:4 as the DNA sequence for coding the aforementioned foreign protein. SEQ ID NO:4 is the DNA sequence which encodes a homologue of bovine lactase dehydrogenase which has been codon optimized for expression in Saccharomyces cerevisiae.

Claim 6 is directed to the transformant according to any of claims 1 through 5, wherein the aforementioned host organism belongs to the Saccharomyces family. Claim 7 is directed to the transformant according to any of claims 1 through 5, wherein the aforementioned host organism is Saccharomyces cerevisiae. Porro et al. teach transformed yeast, Saccharomyces cerevisiae.

Claim 16 is directed to a transformant of the Saccharomyces family into which the DNA for coding a bovine-derived lactate dehydrogenase or its homologue has been controllably incorporated such that the DNA is under the control of a genome promoter of the pyruvate decarboxylase 1 gene on the host chromosome of the Saccharomyces family or such that the DNA is under the control of a structural and functional homologue of the genome promoter of the pyruvate decarboxylase gene, which replaces the genome promoter of the pyruvate decarboxylase 1 gene, and wherein the the pyruvate decarboxylase 1 on the host chromosome has been replaced with the DNA

for coding a bovine-derived lactate dehydrogenase or its homologue. Porro et al. teach, "yeast strains…transformed with at least one copy of a gene coding for lactic dehydrogenase (LDH) functionally linked to promoter sequences allowing the expression of said gene in yeasts" (page 4, lines 6-11). Porro et al. teach, "yeast strains having…a reduced pyruvate decarboxylase activity and transformed with…a gene coding for lactic dehydrogenase (LDH) functionally linked to promoter sequences" (page 4, lines 12-17). Porro et al. teach any yeast promoter…may be used according to the invention…the promoter of pyruvate decarboxylase gene of K. lactis (KlPDC) is particularly preferred (page 14, lines 18-28). Porro et al. further teach, "Pyruvate decarboxylase gene promoters…are particularly preferred" (page 15, lines 2-5). Porro et al. describe making a triple deletion of the pyruvate decarboxylase genes encoding PDC1, PDC5, and PDC6, using homologous recombination (page 8, lines 25-27). Porro et al. further teach that "PDC genes are highly conserved among different yeast genera" (page 9, lines 7-9). Porro et al. also teach "integrative vectors can be obtained by using homologous DNA sequences in certain regions of the host genome, allowing, by homologous recombination, integration of the vector" (page 12, lines 12-15).

Claim 17 is directed to the transformant according to claim 16, wherein the aforementioned host is Saccharomyces cerevisiae. Porro et al. teach transformed yeast, Saccharomyces cerevisiae.

Claim 18 is directed to a lactic acid manufacturing method provided with a process for culturing the transformant described in claim 1, and a process for separating lactic acid from the cultured product obtained in the aforementioned process. Porro et

al. teach, “a process for the preparation of…lactic acid by culturing the above described metabolically engineered yeast strains in a fermentation medium containing a carbon source and recovering lactic acid from the fermentation medium” (page 5, lines 5-10).

Porro et al does not explicitly teach a single embodiment of a transformed bacteria or yeast comprising a DNA for coding a foreign protein having lactate dehydrogenase activity operably linked to a functional homologue of the genome promoter of the pyruvate decarboxylase gene and in which the DNA has been homologously recombined to eliminate the host genome’s pyruvate decarboxylase gene. However, Porro et al. teaches all of the structural elements (transformed yeast and bacteria; introduction of a foreign (bovine) lactate dehydrogenase gene; using a pyruvate decarboxylase promoter for expression of exogenous protein expression; and homologous recombination; knocking out the host genome’s pyruvate decarboxylase gene). However, Porro et al. does not teach knocking out the host genome’s pyruvate decarboxylase gene, by introducing a gene expression cassette in its place.

It would have been obvious to the person of ordinary skill in the art at the time of the invention was made to make a single embodiment of a transformed bacteria or yeast comprising a DNA for coding a foreign protein having lactate dehydrogenase activity operably linked to a functional homologue of the genome promoter of the pyruvate decarboxylase gene and in which the DNA has been homologously recombined to eliminate the host genome’s pyruvate decarboxylase gene.

Regarding the rationale for combining prior art elements according to known methods to yield predictable results, all of the claimed elements were known in the prior

art and one skilled in the art could have combined the element as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Each of the elements (transformed yeast and bacteria; introduction of a foreign (bovine) lactate dehydrogenase gene; using a pyruvate decarboxylase promoter for expression of exogenous protein expression; homologous recombination; knocking out the host genome's pyruvate decarboxylase gene) are taught by Porro et al. and further they are shown to be used for the production of lactic acid. It would be therefore predictably obvious to use a combination of these elements in a recombinant bacteria or yeast.

Regarding eliminating the host genome's pyruvate decarboxylase gene by replacing it with a DNA cassette which includes "a DNA for coding a foreign protein having lactate dehydrogenase activity operably linked to a functional homologue of the genome promoter of the pyruvate decarboxylase gene," it would have been obvious because of a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and commonsense. The prior art teaches the need in the art to solve the problem of optimally producing a recombinant microorganism which has been knocked out for a pyruvate decarboxylase gene and further identifies a number of predictiable potential solutions for making these deletions/ knockouts (by deletion of the gene; deletion or insertion of selectable markers, point-mutations, frame-shift mutations (Porro, page 10, lines 9-24)). One of ordinary skill in the art could have pursued the known potential option (of inserting the DNA cassette

comprising pyruvate decarboxylase promoter/exogenous lactate dehydrogenase gene) with a reasonable expectation of success. It would be therefore predictably obvious to use a alternative method when eliminating the host genome's pyruvate decarboxylase gene.

Furthermore, codon optimization of the bovine lactate dehydrogenase gene for expression in Saccharomyces cerevisiae is well known in the art and therefore obvious.

Therefore the recombinant bacteria or yeast as taught by Porro et al would have been *prima facie* obvious over the recombinant bacteria or yeast of the instant application.

Conclusion

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SDL/ Scott Long
Patent Examiner
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/Janet L. Epps-Ford/

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